NATIONAL INSTITUTES OF HEALTH

FISCAL YEAR 2003

PLAN FOR HIV-RELATED RESEARCH

III: ETIOLOGY AND PATHOGENESIS

PREPARED BY THE OFFICE OF AIDS RESEARCH

AREA OF EMPHASIS:

Etiology and Pathogenesis

SCIENTIFIC ISSUES

In the quest for vaccines to prevent HIV infection and for more effective drugs to contain the infection and treat the opportunistic infections (OIs), tumors, and other manifestations of a dysfunctional immune system, a better understanding is needed of how HIV infection is established and what causes the profound immune deficiency and terrible complications that accompany this infection. What role do the specific products of HIV (the viral genes and their protein products) play in the viral life cycle in individual cells and within the body of infected individuals? How is HIV transmitted between cells and between individuals? What contribution does the immune system make to controlling the infection and to the disease process? What mechanisms are involved in cell injury and death in the immune, nervous, and other systems that HIV afflicts? What host factors and cofactors influence the course and outcome of HIV infection? What is the relationship of HIV infection to the associated malignancies, OIs, neurological impairments, and metabolic disturbances that characterize AIDS? These outstanding questions define the central contemporary issues encompassed within the area of etiology and pathogenesis research.

HIV BIOLOGY

Since the initial isolation of HIV in 1983 and its identification as the causative agent of AIDS shortly thereafter, tremendous progress has been made in understanding the genetic structure and variability of the viral genome, the critical aspects of the virus life cycle, and the functions of viral gene products and their interaction with the host. The knowledge that has emerged from basic research in these areas has provided and

continues to provide the foundation for all efforts to develop current therapies to treat HIV infection. The elucidation of the structure and function of two of the critical viral enzymes—reverse transcriptase and protease—has represented a critical step in the development of effective anti-HIV drugs. Similar insights from basic research into the mechanisms of viral entry and the mechanisms by which the infection becomes established and spreads also are crucial for vaccine and microbicides development efforts.

The challenges remain to develop new drugs for the treatment of HIV infection that are cheaper, easier to take, more potent, and with fewer adverse effects than those currently in use, along with microbicides to prevent sexual transmission of HIV infection; and to identify immunogens able to elicit strong neutralizing responses for the development of an effective vaccine.

Scientific advances in AIDS research, such as the resolution of the crystal structure of gp41 and gp120 bound to CD4 and a neutralizing antibody, the delineation of many of the molecular interactions between virally encoded regulatory proteins and host cell factors, recent insights into critical requirements for viral attachment and replication, and the identification of conserved structural intermediates of gp41 that might be able to elicit a strong and cross-reactive neutralizing response are affording us the opportunity to identify new viral and cellular targets for therapeutic and preventive interventions.

PRIORITY FOR FUTURE RESEARCH:

- **Facilitate the translation of new insights into HIV biology to develop novel interventions for the prevention and treatment of HIV infection.**

TRANSMISSION, ESTABLISHMENT, AND SPREAD OF HIV INFECTION

Emphasis should be placed on the elucidation of structures and a better understanding of the biochemistry, interaction, and biologic function of relevant virus and host cell constituents. These studies should focus on defining the roles of specific host cell and viral gene products in HIV replication, persistence, and pathogenesis. NIH also should play an instrumental role in facilitating collaborative research aimed at developing and implementing biologically relevant validated assays for drug screening.

In spite of the tremendous scientific advances in AIDS research, the factors that determine the transmissibility of HIV and the variables that may influence a person's susceptibility to HIV infection following exposure have yet to be clearly understood. The observed resistance to HIV-1 infection of multiply-exposed subjects bearing a homozygous deletion in one of the

genes encoding a chemokine coreceptor for primary HIV-1 isolates highlighted the importance of coreceptors in HIV-1 transmission. Intriguing new data have also showed that a novel dendritic cell (DC)-specific C-type lectin termed DC SIGN plays an important role in establishing the first contact between DC and resting T-cells. Altogether these findings clearly suggest that the early interaction of HIV with target cells at the portal of entry is critical for the subsequent establishment and spread of infection.

Prospective studies in discordant couples have recently provided evidence that peripheral blood viral load is the most important predictor of the risk of heterosexual transmission of HIV. These findings have important implications for the development of prevention strategies, since they suggest that reducing viral load in HIV-infected persons will result in their decreased infectiousness. In the same studies, circumcision also appeared to prevent acquisition of HIV, highlighting the role of biologic factors as well as behavior in HIV transmission.

NIH-funded research is giving special emphasis to studies aimed at defining the role of components of the mucosal compartment, cellular and molecular aspects of mucosal innate and adaptive immunity, viral and host genetic factors, and cofactors such as other infectious agents, sexually transmitted diseases (STDs), and local inflammatory processes, on HIV-1 acquisition and transmission. This basic knowledge is crucial for our efforts to develop effective vaccines and microbicides. In the developing world, where infection rates have climbed to more than 20 percent in some countries and few people can afford antiretroviral drugs, the main issue continues to be how to stop transmission of the virus by effective preventive interventions.

PRIORITY FOR FUTURE RESEARCH:

- **Elucidate the biologic determinants of HIV transmission between individuals and define the mechanisms by which host factors, viral factors, and cofactors may influence the process of virus transmission.**

Emphasis should be placed on studies focused on cohorts that are most representative of the expanding HIV epidemic. This can be facilitated by studies whose design reflects the collaborative interaction of basic scientists and population-based researchers.

Efforts should be directed at understanding the relative efficiency of transmission of cell-free and cell-associated virus in various bodily fluids at different portals of entry (particularly mucosal), mechanisms and timing of initial entry, the cells that represent the first target of infection, mechanisms

of virus compartmentalization in genital secretions, the relationship between biologic findings and the anatomical organization of mucosal tissue, and the role of viral genotypes/phenotypes and dose on HIV entry and establishment of infection. There also should be an emphasis on enabling the availability of emerging technologies in genetics, functional genomics and proteomics, and the assessment of host immune responses for studies of the biology of HIV transmission.

PATHOGENIC MECHANISMS OF HIV INFECTION

Ongoing research at NIH on the molecular, cellular, and organ system levels is elucidating the pathogenic mechanisms of HIV infection. Research at the cellular and molecular levels includes studies of the mechanisms by which HIV infects various cell types, the interaction between the viral regulatory elements and host cell factors that appear to be directed at maintaining a persistent infection, and the viral- and host-mediated mechanisms that influence the level of viral expression seen in successive stages of HIV disease. Since HIV so profoundly affects the immune system, ongoing research also is aimed at elucidating the viral- and immune-mediated pathogenic processes that result in the severe loss of immune function, the inappropriate immune activation, and the disruption of immunomodulatory cytokine production and regulation observed in HIV infection and disease.

NIH-supported investigators have demonstrated that significant levels of virus are present in plasma during all stages of HIV infection, including the clinically asymptomatic phase, and that active virus replication is directly linked to the depletion of T-cell populations in infected individuals and correlates with progression to disease. This model of AIDS pathogenesis would imply that HIV induces disease by replicating at high levels in CD4+ T cells, eventually weakening the immune system and causing it to fail. However, simian immunodeficiency virus (SIV) replicates at high levels in the blood of infected African green monkeys without causing any symptoms or disease, clearly indicating that high levels of viremia do not necessarily lead to disease. Host factors or the particular nature of the host response play a critical role in determining whether and when disease arises following infection. Interaction of HIV with its host is a dynamic process that varies through the course of infection from the very early to the late stages. Structured treatment interruptions appear to be very effective at stimulating antiviral immune responses and controlling viral rebound in patients during primary HIV infection but not in patients with more chronic infections. CD4+ T-cell helper activity diminishes rapidly after primary HIV infection and is not restored by effective antiviral therapies administered at a later time. Studies of host-virus interaction *in vivo* at different stages of HIV infection and disease have great implications for a better understanding of

the effects and nature of the host response to HIV, the processes leading to the loss of control of HIV replication, and the pathogenesis of AIDS.

PRIORITY FOR FUTURE RESEARCH:

- **Characterize the dynamic of virus-host interaction through the course of HIV infection.**

The dramatic success of effective antiretroviral therapies in reducing plasma viremia to undetectable levels had raised the intriguing possibility that prolonged therapy might lead to virus eradication. However, recent data have indicated that the virus can persist in the body of HIV-infected patients for almost a lifetime. HIV can persist in a latent reservoir of resting memory CD4 T cells that is established very early after infection and by continuously replicating, albeit at very low levels, even in the presence of antiretroviral therapies able to drive viral load below the limits of detection. The continuous ongoing viral replication might explain the apparent long half-life of the latently infected reservoir, since this could be continuously reseeded from activated CD4 T cells and monocytes/macrophages newly infected with HIV. Monocytes and macrophages also appear to represent a significant reservoir for viral replication in patients on antiretroviral therapies. A better understanding of the different mechanisms of viral persistence is needed to understand the reasons for drug failure, to design rational approaches for virus control or eradication, and to better assess the impact of persistence on HIV transmission and its implications for HIV prevention.

PRIORITY FOR FUTURE RESEARCH:

- **Investigate the mechanisms of persistence of HIV infection.**

Research efforts should focus on the explication of the cells and tissue reservoirs of persistent virus replication and their rates of turnover, the mechanisms of viral latency and reactivation, the impact of low-level viral replication on virus transmissibility, and the ability of natural and induced immunity to control and eliminate persistent infections.

The new emphasis on the dynamic and quantitative aspects of HIV replication is also paralleled by new efforts to quantitate T-cell population dynamics *in vivo* during different stages of HIV infection and disease. These efforts have great implications for understanding the mechanism behind the most central and unresolved issues in HIV-mediated immunopathogenesis: the depletion of CD4+ T cells and the failure of the regenerative capacity of the immune system to compensate for virus-induced

damage. Several mechanisms, either direct or indirect, have been suggested; however, the critical mechanism remains to be elucidated. New technological developments that permit investigators to measure lymphocyte population dynamics and numbers of cells recently emigrated from the thymus during HIV infection, disease, and therapy may provide valuable insights into this pathogenic process.

PRIORITY FOR FUTURE RESEARCH:

- **Define the direct and indirect mechanisms that lead to T-cell depletion following HIV infection and the factors that determine numerical and functional reconstitution of T-cell populations in response to therapy.**

Elucidation of these mechanisms will be critical for generating new therapeutic principles and approaches that will take into account both viral and cellular kinetic parameters. Potential compensatory mechanisms to replenish the lost T cells include peripheral expansion of residual memory cells and increased production of naive cells by the thymus. Current effective antiretroviral therapies lead to a rapid increase in memory CD4 and CD8 T cells, probably due to redistribution from lymphoid organs, a decrease in cell death, and peripheral expansion. However, regeneration of the T-cell repertoire is generally delayed for many months and will ultimately require production of new T cells from the thymus.

Understanding the normal development and functioning of the human immune system is crucial to our ability to understand the effects of HIV on the immune system and the pathogenesis of AIDS. This understanding also holds the key to designing rational immune reconstitution approaches in persons undergoing antiretroviral treatment and identifying the characteristics of the immune response that are needed for a protective vaccine. The phenomenal discoveries in immunology of the last decades have been built on studies of the mouse immune system. While important lessons can be learned from these experimental studies, not all findings from the mouse model can be directly translated to the human system because of its heterogeneity and complexity.

PRIORITY FOR FUTURE RESEARCH:

- **Enhance and expand innovative studies of human immunology to guide vaccine development and immune reconstitution efforts.**

Emphasis should be placed on a better understanding of the elicitation and maintenance of immunologic memory. Emphasis also should be given to the definition and validation of markers and assays that will enhance our understanding of and ability to study immune function in humans, especially those approaches that permit the study of the *in vivo* regulation and function of the immune system. Recent technological breakthroughs are affording us the opportunity to more accurately assess the quantity and function of T cells in HIV infection. These are the tetramer technique that allows the analysis of antigen-specific CD8 T cells during the infection process, the nonradioactive method that directly measures lymphocyte turnover in humans, the ELISPOT assay that measures the secretion of cytokines in response to an antigenic stimulus, the single-cell intracellular cytokine production assay, and the deletion circles technique that enables the identification of T cells recently emigrated from the thymus. The use of these innovative techniques is already providing HIV investigators with critical insights into the effects of HIV infection, antiretroviral therapy, and potential preventive or therapeutic vaccines on the immune system. Our attempts at preserving or reconstituting immune function in HIV-infected persons also will benefit from focused efforts directed at elucidating the homeostatic and regenerative mechanisms of lymphocyte populations, the markers for true thymic-derived cells, the factors that may influence T-cell proliferative capacity or survival in the normal state and with HIV disease, the immunological impact of long-term therapies, and potential interventions to improve thymic function and the generation of naive T cells. Likewise, focused efforts directed at characterizing the functional diversity of CD8 effector cells, at analyzing humoral and cellular immunity in microenvironments (especially at mucosal sites), and at a better understanding of mechanisms leading to maintenance of immunological memory will greatly benefit research aimed at developing effective HIV vaccines.

Continued support of *in vivo* research is a high priority at NIH in order to further an understanding of the interaction between the virus and host immune system response. NIH-sponsored longitudinal cohort studies constitute a major resource for pathogenesis research. Specific cohorts, such as long-term nonprogressors, HIV-exposed but uninfected individuals, and rapid progressors, will provide clues for treatment and vaccine research by helping to characterize immune response profiles and by providing information on correlates of immunity. *In vivo* research into mechanisms of virus-mediated immunopathogenesis also utilizes animal models. All the available animal models, but in particular the nonhuman primate models, have contributed and continue to contribute to our understanding of disease mechanisms.

In response to the changing demographics of HIV infection, studies have been designed to elucidate the pathogenic mechanisms more commonly observed in women, children, and adolescents infected with HIV. As part of this effort, NIH supports a number of epidemiologic cohort studies focused specifically on women, adolescents, and children. The study of patient samples and of data generated by these cohorts is providing critical information about the mechanisms of transmission, the course of disease progression, and response to therapy in these populations.

The basic science underlying HIV etiology and pathogenesis research is generally gender neutral. Basic mechanisms of viral replication and pathogenesis are not expected to differ in women and men. However, there are differences in the way HIV infection is transmitted and how the disease is manifested in women and men. Moreover, recent studies have highlighted differences in viral dynamics in women compared with men, and further studies are warranted to elucidate the biological underpinnings for these findings. Some of the studies that examine gender differences compare factors other than sex in patients. HIV-infected women are more likely to be poor, to belong to racial minorities, to be of poor health status, and to use injection drugs. These are all factors that might have important effects on health outcomes for both men and women infected with HIV. Age also is emerging as an important factor to consider, due to the increased survival of HIV-infected persons and the increase in newly HIV-infected individuals at different life stages.

PRIORITY FOR FUTURE RESEARCH:

- **Investigate the impact of gender, health status, race, and age on the biology of HIV infection and on the responses to therapies and vaccines.**

DISEASE MANIFESTATIONS

HIV infection affects the functioning of virtually all the organ systems within the body. Current NIH-supported basic and clinical studies are focused on the characterization of HIV/AIDS-associated diseases and on the assessment of their relative contribution to the overall disease progression in AIDS. NIH is striving to enhance the bidirectional flow between basic and clinical observations and intervention programs on HIV-related complications.

The availability of new and more effective antiviral drugs and treatment modalities is having a beneficial effect on the course of HIV infection and has altered the incidence and nature of some of its manifestations. The influence of new antiretroviral therapies, which are able to lower viral

load to undetectable levels, on the natural history of AIDS is providing an unprecedented opportunity to gain insights into the pathogenic mechanisms underlying the disease manifestations associated with HIV infection and AIDS. Unfortunately, use of these therapies also is associated with a series of side effects and complications that we are just starting to appreciate and study.

Metabolic and Body Composition Changes

The study of HIV-associated manifestations is rapidly changing as a result of the introduction of effective antiretroviral therapies and the concomitant decline in the incidence of OIs. The incidence of wasting has declined, and insulin resistance, hypercholesterolemia, hypertriglyceridemia, and abnormal fat distribution (either depletion or accumulation) have been described in HIV-infected individuals taking antiretroviral therapies. These manifestations are a real cause for concern with broad public health implications. Patients are experiencing problems in adhering to regimens when these symptoms occur: some stop taking medications, and others are not initiating therapies due to the possible occurrence of disfiguring physical changes and the long-term risk of cardiovascular complications. These changes were initially considered a single syndrome commonly referred to as lipodystrophy. Recent data are instead suggestive of multiple syndromes with different etiologies. Protease inhibitors were first associated with these metabolic and body composition changes, but recent data have indicated that HIV patients treated with only nucleoside reverse transcriptase inhibitors (NRTIs) also develop these symptoms. In addition to the direct effects of these drugs, age, duration of therapy, HIV disease, and return to health following suppression of viral replication also may play a role in the development of these abnormalities. With the longer duration of therapy, many other complications have been reported in association with current anti-HIV treatment including bone disease, lactic acidosis, pancreatitis, and liver toxicities. Mitochondrial damage and depletion resulting from the inhibitory activity against gamma DNA polymerase of some of these drugs could potentially be involved in the etiology of some of these complications.

PRIORITY FOR FUTURE RESEARCH:

- **Advance the understanding of the mechanisms responsible for the toxicities and long-term complications of antiretroviral therapy and the factors that underlie changes in the causes of morbidity and mortality in an era of increasingly effective therapies.**

Elucidation of the factors contributing to metabolic and body composition changes, toxicities, and long-term consequences of antiretroviral therapy will allow effective therapies to be tailored to the specific mechanism by which they occur, with the potential for enhancing quality of life in HIV-infected persons.

Although the incidence of wasting has declined, it remains one of the most devastating aspects and one of the major causes of morbidity and mortality in HIV-infected individuals who do not respond or lack access to potent antiretroviral therapies, an issue in the developing countries. Weight loss in AIDS results in a significant reduction in survival, independent of other influencing factors, including CD4 cell count and history of infection or malignancy.

The introduction of effective antiretroviral therapies has changed the natural history of HIV infection and has led to a dramatic decline in morbidity and mortality in HIV-infected persons in developed countries. However, anti-HIV therapy is not a cure and does not successfully benefit every infected individual. End-stage liver disease and liver failure are becoming an increasing cause of mortality in HIV-infected patients. However, since multiple concurrent causes of liver damage are associated with HIV infection including hepatitis viruses coinfection, antiretroviral hepatotoxicities, OIs, and cancers, the impact of each cause of liver injury on a patient's survival in an era of effective therapies is unclear. Epidemiological studies in large cohorts will be instrumental in identifying changes in the causes of morbidity and mortality as a result of the availability of effective therapies in HIV-infected communities and in providing us with useful insights into their etiologies.

AIDS-Related Malignancies

AIDS is associated with a broad spectrum of neoplasms, including Kaposi's sarcoma (KS), lymphomas, human papillomavirus (HPV)-related cervical and anogenital carcinomas, Castleman's disease, leiomyomas, leiomyosarcomas, and hepatitis B-related hepatocellular carcinomas. Because HIV causes immunosuppression and because most AIDS-associated malignancies are strongly associated with viruses, HIV infection provides a unique model to study the interplay of viruses, a dysfunctional immune system, and the development of cancers. NIH-supported investigators are trying to clarify the mechanistic role of chronic stimulation mediated by viral and cellular proteins, high levels of growth-promoting cytokines present in HIV-infected subjects, and human DNA and RNA viruses and their direct or indirect interaction with HIV in the development of AIDS-associated malignancies. Studies of AIDS-related KS have highlighted the

potential causative role of a newly discovered human herpes virus (HHV-8), angiogenic growth factors, and HIV proteins released in the extracellular milieu in the etiology of this neoplasm. Elucidation of the interactive factors involved in the pathogenesis of AIDS-associated malignancies will possibly translate to the identification of new targets for prevention and treatment.

Following the introduction of effective antiretroviral therapies, preliminary studies have shown a dramatic decline in the incidence of KS, but no decrease in non-Hodgkin's lymphoma (NHL) or other AIDS-related malignancies has been reported. More extensive followup is needed to clearly discern the impact of effective therapy and prolonged survival of HIV-infected persons on their risk of developing cancer.

Neuropathogenesis

Neurological disease and neurobehavioral dysfunction associated with HIV infection cause considerable morbidity and mortality in afflicted children and adults. These manifestations include diseases associated with opportunistic infection of the brain resulting from the underlying immunodeficiency and the AIDS dementia complex, a disorder that is unique to HIV infection. HIV enters the central nervous system (CNS) very early during infection, although manifestation of neurologic impairment occurs in late-stage HIV infection. Intense research efforts have focused on elucidating the role of HIV persistence in the brain parenchyma in the development of CNS disease. The cells expressing HIV or SIV in patients or monkeys with AIDS have been found to be primarily perivascular macrophages, that is, cells derived from monocytes trafficking to the brain that have a very rapid turnover. These findings raise the intriguing possibility that the viral reservoir in the CNS is not composed of persistently or latently infected cells but of cells undergoing continual turnover. NIH-supported research is directed at understanding how HIV infection contributes to nervous system damage through direct interaction of HIV with neuronal and nonneuronal cells and indirect mechanisms, such as those mediated by cytokines, chemokines, and neurotoxins released in response to the infection or the local inflammatory response to the infection. Important areas of ongoing research include the determination of how HIV enters and establishes infection in the different compartments of the CNS and the correlation between the extent of HIV replication *in vivo* and the incidence and severity of neurologic complications. The possible role of the CNS as a reservoir of HIV infection in the setting of antiretroviral therapies with limited CNS bioavailability also is under investigation. Special emphasis in all these studies is given to *in vivo* models of neuropathogenesis and to the

integration of basic research studies on the neurologic complications of AIDS with natural history studies and ongoing clinical trials.

Opportunistic Infections and Co-infections

HIV infection results in progressive damage of the immune systems of infected individuals and makes them susceptible to a diverse collection of bacteria, viruses, fungi, and protozoa that represent the major causes of suffering and death for HIV-1-infected individuals. OIs can affect virtually every tissue and organ system in the body, resulting in severe functional compromise. NIH currently supports a comprehensive portfolio of basic research on the pathogenesis of AIDS-associated OIs. Currently supported research is directed toward developing methods to culture and grow these pathogens *in vitro*, developing animal models to study disease pathogenesis, sequencing these infectious microorganisms' genomes, identifying new targets for therapeutic interventions, and facilitating discovery and development of prophylactic and therapeutic agents. Special emphasis is given to the interactions between the pathogen and the host and its immune system. This research will permit a better understanding of the establishment of infection, mechanisms of immune control by the host, evasion by the pathogen, and the contribution of the host immune response to disease.

The use of potent antiretroviral therapies has resulted in a dramatic decline in the incidence of OIs, suggesting that the increase in the number of immune cells that follows effective antiretroviral therapies is accompanied by the recovery of functional responsiveness to antigens of several important opportunistic pathogens. However, development of OIs during the first 2 months of effective antiretroviral therapy has also been described, suggesting that the restoration of immune function may be partial or delayed. As a result of reconstitution of their immune responses, new manifestations also have been reported in HIV-infected persons taking anti-HIV drugs.

OIs remain one of the most important complications of HIV infection and the principal cause of death in AIDS patients. Understanding the fundamental biology and pathogenesis of these organisms, their interaction with the host immune system, and the effect of therapy-associated immune reconstitution on the clinical course and manifestations of OIs will translate into new or more rational approaches to the prevention and treatment of OIs in patients on antiretroviral therapy, as well as in patients who lack access to or who are not responding to antiretroviral therapies.

As the classic OIs that were the hallmark of HIV/AIDS have increasingly become less frequent as a result of the introduction of effective antiretroviral

therapies and the use of opportunistic infection prophylaxis, co-infections have emerged as important complications in HIV infection. Hepatitis B and C virus (HBV and HCV) coinfections are becoming increasingly prevalent in HIV-infected patients in developed countries, and epidemiologic studies have indicated that chronic liver disease now represents a major cause of morbidity and mortality in this population. Worldwide, tuberculosis (TB) is a key co-infection suffered by the HIV-infected, and the numbers of TB cases in the world are rising, driven in large part by the HIV epidemic. There is a clear need to conduct research directed at assessing the impact of co-infections on immune dysfunction and HIV progression and likewise the impact of HIV infection on the natural history and pathogenesis of co-infecting pathogens.

Organ System-Specific Complications of HIV Infection

Organ system-specific manifestations also attend HIV infection and disease. Gastrointestinal dysfunction and malabsorption are commonly observed in HIV-infected subjects. The gastrointestinal tract is one of the most important routes of transmission of HIV and appears to be a major site of viral replication and the major site of CD4+ T-cell depletion in early stages of infection in the SIV model. NIH-supported researchers are investigating the contribution of OIs, of micronutrient deficiencies, of acquired deficiencies in intestinal enzymes, of malignancies, and of potential HIV infection of cells in the gastrointestinal tract to the gastrointestinal complications observed in HIV-infected individuals. HIV infection is also associated with multiple endocrine alterations, probably reflecting critical interaction between the endocrine and the immune systems. HIV-associated hematologic, pulmonary, cardiac and vascular, renal, mucocutaneous, and liver complications also represent a cause of morbidity in infected subjects. The pathogenic mechanisms involved in all these AIDS manifestations are not well understood and are under investigation. Their definition will permit a more rational approach to both preventive and therapeutic interventions.

SCIENTIFIC OBJECTIVES AND STRATEGIES

OBJECTIVE:

Delineate the viral, host, and immune mechanisms involved in the transmission, establishment, and spread of HIV infection in diverse populations across the spectrum of age, gender, and national and international settings.

- Determine the role of viral phenotype/genotype and dose on transmission of cell-free and cell-associated virus, in various bodily fluids at different portals of entry.
- Determine mechanisms by which virus-encoded genes and viral gene products regulate HIV replication and influence transmission, establishment, and spread of HIV infection.
- Determine the structures and interactions of viral and host proteins that are important for the transmission, establishment, and spread of HIV infection.
- Delineate the mechanisms by which host-encoded genes and gene products regulate HIV replication and influence transmission, establishment, and spread of HIV infection.
- Determine the cell molecules and tissue types that serve as portals of entry and support subsequent spread of HIV.
- Delineate the mechanisms by which innate and adaptive immunity influence HIV replication and modulate transmission, establishment, and spread of HIV infection.
- Delineate the mechanisms by which co-infections influence HIV replication, transmission, establishment, and spread of HIV infection.
- Evaluate the influence of prevention and treatment on the early events in HIV transmission, establishment, and spread.

To facilitate the research goals listed above:

- Facilitate the translation of new insights from structural biology, computational biology, genomics, and proteomics to understand the etiology and pathogenesis of HIV infection.

- Further develop and utilize experimental human, nonhuman, *ex vivo*, and theoretical/mathematical models to study the transmission and establishment of lentiviral infections with emphasis on models of direct relevance to human HIV infection and models that address important issues not readily approachable in human subjects.
- Promote augmented access to and sharing of key patient samples, animal model resources, laboratory reagents, new technologies and equipment, information databases, and quantitative virologic and immunologic assays.
- Support and expand innovative research on the transmission, establishment, and spread of HIV infection.
- Develop and utilize natural and innovative technologies to procure, maintain, and expand the macaque model of AIDS.

OBJECTIVE:

Delineate the viral and host mechanisms associated with the pathogenesis of immune dysfunction and disease progression in diverse populations across the spectrum of age, gender, and national and international settings.

- Determine the impact of early events in the establishment and systemic spread of HIV infection on the clinical course of the disease.
- Define the virologic, host, pharmacologic, co-pathogens, and environmental factors that contribute to disease progression and nonprogression.
- Define the virologic and host factors that enable HIV to establish and maintain a persistent infection *in vivo* in the setting of both drug-naive and drug-treated individuals.
- Delineate the mechanisms of host immune control of HIV replication and investigate how the effectiveness of immune control may vary through the course of infection, upon the identity and location of infected host cells, and upon the influence of therapeutic interventions.
- Delineate the molecular mechanisms by which virus-encoded genes, viral gene products, and host cellular factors regulate HIV replication and influence pathogenesis.
- Determine the factors that influence the susceptibility of target cells to HIV infection and their ability to support HIV replication.
- Determine the structures of viral and host proteins involved in the processes that underlie disease progression.
- Delineate the direct and indirect mechanisms underlying HIV-induced depletion and dysfunction of immune target cells/tissues, focusing on:
  - the loss of specific CD4+ T lymphocyte subpopulations and clones;
  - the impact of HIV infection on T-cell population numbers, specificities, and functions;

  - virally-triggered immunopathogenesis, including immune activation, cell death, induction of nonresponsiveness, dysregulation in the number and function of immune effector cells other than T lymphocytes, and production of host factors, including cytokines and other mediators;
  - the structural and functional compromise of primary and secondary lymphoid organs including hematopoietic precursers cells and their microenvironment;
  - influences on the developing immune system; and
  - disruption of host compensatory mechanisms that govern the generation, regeneration, and homeostasis of T-cell populations.

- Evaluate whether and to what extent viral-induced damage to the immune system can be reversed following suppression of HIV replication by therapeutic interventions.

- Determine the life span and developmental and regenerative pathways of T lymphocytes; elucidate the mechanisms that regulate the size and composition of T-cell populations and how these may change with age.

- Define markers and functional assays that will enhance our understanding of and ability to study innate and adaptive immune function in humans, especially those approaches that permit study of the *in vivo* activity of the immune system.

- Define the reservoirs of virus infection that permit HIV persistence throughout the course of HIV infection, including in the setting of therapies and in the presence of ongoing immune responses.

- Determine the viral and host factors associated with clinical response and lack of response to therapeutic interventions in HIV-infected subjects.

To facilitate the research goals listed above:

- Further develop and utilize experimental human, nonhuman, *ex vivo*, and theoretical/mathematical models to study the pathogenesis of lentiviral infections with emphasis on models of direct relevance to human HIV infection and models that address important issues not readily approachable in human subjects.

- Promote augmented access to and sharing of key patient samples, animal model resources, laboratory reagents, new technologies, and equipment, information databases, and quantitative virologic and immunologic assays.
- Facilitate the translation of new insights from structural biology, computational biology, genomics, and proteomics to understand the immunopathogenesis of HIV infection.
- Enable the translation of basic and preclinical research findings into clinical studies in humans to advance the understanding, treatment, and prevention of HIV infection.

OBJECTIVE:

Define the etiology, pathophysiology, and consequences of HIV infection and treatment-related metabolic and body composition changes in diverse populations across the spectrum of age, gender, and national and international settings.

- Define the mechanisms underlying alterations in metabolism, body composition, growth and development, and the risks of atherosclerotic, cardiovascular, vascular, and bone disease:
  - to determine the effects of antiviral therapies and suppression of virus replication;
  - to determine the influence of disease stages;
  - to determine the contributions of individual virologic and host factors; and
  - to determine the contributions of OI, hormonal dysregulation, and other consequences of HIV infection.
- Employ therapies that effectively suppress HIV replication to probe the pathogenic mechanisms underlying alterations in metabolism, body composition, growth and development, and the long-term risks of diabetes, bone disease, and atherosclerotic cardiovascular disease.
- Determine factors associated with clinical response or lack of response to therapeutic interventions against AIDS-associated metabolic and body composition changes, impaired growth and development, and the long-term risks of diabetes, bone, and atherosclerotic cardiovascular disease.

To facilitate the research goals listed above:

- Transfer expertise from the endocrine, metabolic, cardiovascular, and bone research field to the HIV field and promote linkage between HIV researchers and established individuals and centers of excellence in these areas of research.
- Promote programs to facilitate access to and sharing of patient samples, animal model resources, reagents, new technologies, equipment, information databases, and modeling/calculation tools used in metabolic, cardiovascular, and bone research.

- Facilitate the translation of new insights from structural biology, computational biology, genomics, and proteomics to understand the metabolic, endocrine, vascular, and bone disease complications associated with HIV infection and treatment.
- Support the development of new and improved research techniques to address the emerging metabolic, endocrine, cardiovascular, and bone complications.
- Integrate metabolic, endocrine, cardiovascular, and bone studies into ongoing and planned treatment trials.

OBJECTIVE:

Elucidate the etiologic factors, co-factors, pathogenesis, and consequences of HIV-related malignancies in diverse populations across the spectrum of age, gender, and national and international settings.

- Elucidate the role of HIV infection and its associated immune dysfunction in the development of HIV-associated malignancies.
- Elucidate the role of infectious agents other than HIV, including novel pathogens, in the development of HIV-associated malignancies and develop new methodologies for novel pathogen identification.
- Define the biologic processes underlying transmission and pathogenesis of infectious pathogens associated with AIDS-related malignancies.
- Identify the mechanisms by which immune dysfunction, oncogenes, suppressor genes, carcinogens, and non-HIV viral and other microbial genes and proteins contribute to the development of HIV-associated malignancies; correlate these molecular factors with epidemiologic studies.
- Identify the characteristics of the host that modulate the risk of HIV-associated malignant disease.
- Determine the role of immunologic control to infectious etiologic agents in their susceptibility to AIDS-associated malignancies.
- Employ therapies that effectively suppress HIV replication to probe the pathogenic mechanisms of HIV-related malignancies, and evaluate how the manifestations of HIV-associated malignancies are altered by such therapies.
- Determine factors associated with clinical response and lack of response to antineoplastic therapeutic intervention in HIV-infected subjects.

To facilitate the research goals listed above:

- Promote programs to facilitate the development of and augmented access to *in vivo* animal models, patient specimens for HIV-associated malignancies, sharing of key patient samples, laboratory reagents, new technologies and equipment, information databases, and quantitative virologic and immunologic assays.

- Facilitate the translation of new insights from structural biology, computational biology, genomics, and proteomics to understand the etiology and pathogenesis of AIDS-related malignancies.

OBJECTIVE:

Elucidate the mechanisms and consequences of HIV-associated neurological disease and neurobehavioral dysfunction in diverse populations across the spectrum of age, gender, and national and international settings.

- Determine the cellular and molecular bases and pathogenic mechanisms involved in HIV-associated neurobehavioral and neurological dysfunction including:
  - identifying how HIV enters, establishes infection, spreads, and persists in the CNS;
  - examining the effects of HIV infection on specific cell populations and regions of the nervous system;
  - investigating the connection between blood-brain barrier dysfunction and neuronal injury;
  - determining the relationship of virologic, host (including the genetics of the virus/host interactions), pharmacologic, and environmental factors to HIV-associated neurologic dysfunction (including peripheral neuropathies);
  - determining the consequences of the biological activity of cytokines, other mediators, and their receptors on the neurologic tissue in the context of HIV infection; and
  - developing methods to monitor the levels of HIV replication and consequences of HIV infection within the CNS of living subjects.
- Determine factors associated with clinical response and lack of response to therapeutic interventions for neurologic and neurobehavioral complications of HIV disease.
- Determine the host and viral factors influencing independent evolution of drug-resistant HIV strains in the CNS compartment.
- Determine the impact of HIV/CNS infection on systemic disease progression.
- Determine the role of the CNS as a reservoir of, and sanctuary for, persistent HIV infection.
- Define mechanisms of immunologic control of HIV and OIs in the CNS.

- Develop methods to investigate, diagnose, and monitor HIV-associated neurological and neurobehavioral disorders.
- Investigate aspects of HIV infection that uniquely influence the developing nervous system.
- Delineate the role of OIs, other disease complications, and drug treatment in neurologic and neurobehavioral complications of AIDS including CNS dysfunction and peripheral neuropathies.
- Employ therapies that effectively suppress HIV replication to probe pathogenic mechanisms of HIV-associated neurologic diseases and neurobehavioral dysfunction; evaluate how the manifestations of HIV-associated neuropathogenesis are altered by such therapies.

To facilitate the research goals listed above:

- Develop and employ appropriate animal models (e.g., nonhuman primate models) of CNS-lentivirus infection that best reflect specific aspects of the human HIV/CNS disease course on treatment that are crucial to understanding neurobehavioral and neurologic disorders.
- Ensure that information, materials, and specimens needed for neuro-AIDS research are appropriately collected, catalogued, classified, stored, and distributed, and promote access to and sharing of new technologies and equipment.
- Encourage new multidisciplinary approaches to investigate HIV-associated neurological disease and neurobehavioral dysfunction.
- Improve existing and develop new technologies for biochemical markers and the imaging of neurologic dysfunction.
- Facilitate the translation of new insights from structural biology, computational biology, genomics, and proteomics to understand HIV-related neurologic disease.
- Integrate neurologic studies into the planning and conduct of treatment trials.

OBJECTIVE:

Elucidate the pathogenic mechanisms and consequences of OIs and co-infections (especially HBV, HCV, TB, and HPV) in HIV-infected individuals in diverse populations across the spectrum of age, gender, and national and international settings.

- Conduct studies of the basic biology and pathogenic mechanisms of opportunistic pathogens and their interactions with the host, including definition of:
  - normal flora;
  - portals of entry of opportunistic pathogens into the human host;
  - processes that underlie the establishment and spread of infection; and
  - mechanisms of tissue and organ system damage.
- Identify and elucidate the genetic and environmental risk factors associated with susceptibility to, the development of, and the progression of OIs.
- Study the effects of OIs and co-infections on immune dysfunnction and HIV disease progression.
- Study how HIV infection changes the natural history and pathogenesis of the co-infecting pathogens.
- Elucidate the mechanisms of immune function that mediate protection against OIs.
- Study the effects of HIV therapy-associated immune reconstitution on the clinical course and manifestation of OIs and co-infections.
- Characterize the molecular and phylogenetic relationships of major AIDS OIs, pathogens; standardize and improve techniques of phylogenetic analysis; and integrate strain-specific characterization of data into studies of the pathogenesis, mechanisms of transmission, and epidemiology of OIs.
- Employ therapies that effectively suppress HIV replication to probe the pathogenic mechanisms of HIV-associated OIs, and evaluate how the causes, agents, and manifestations of these HIV-associated infections are altered by such therapies.

- Determine factors associated with clinical response and lack of response to therapeutic interventions against OIs and co-infections in HIV-infected subjects.
- Study clinical syndromes seen in HIV-infected persons that are not associated with known opportunistic pathogens in order to identify novel pathogens and characterize their biology and pathogenic mechanisms.

To facilitate the research goals listed above:

- Facilitate the translation of new insights from structural biology, computational biology, genomics, and proteomics to understand the etiology and pathogenesis of HIV co-infections and HIV-related OIs.
- Develop and validate assays of opportunistic pathogen-specific immune responses.
- Develop *in vitro* techniques and animal models to propagate and define the life cycles of the opportunistic pathogens associated with HIV disease.
- Develop and validate diagnostic assays for the reliable and rapid identification of HIV-associated OIs.

OBJECTIVE:

Elucidate the etiology, pathogenesis, and consequences of HIV-related organ-specific disorders in diverse populations across the spectrum of age, gender, and national and international settings.

- Investigate the etiologic and pathogenic mechanisms and consequences of HIV-associated:
  - gastrointestinal, including liver and biliary diseases,
  - nephropathy,
  - endocrine dysfunction,
  - hematologic disorders,
  - pulmonary disorders,
  - autoimmune disorders,
  - cardiac and vascular disease,
  - cutaneous disease,
  - oral disease, and
  - other organ/tissue-specific disorders.
- Employ therapies that effectively suppress HIV replication to probe the pathogenic mechanisms of HIV-related organ/tissue-specific complications, and evaluate how the manifestations of HIV-related organ/tissue-specific complications are altered by such therapies.
- Determine factors associated with clinical response and lack of response to therapeutic interventions against HIV-related disorders.
- Employ animal models to investigate the etiology and pathogenesis of lentivirus-associated disorders in the above systems.

To facilitate the research goals listed above:

- Facilitate the translation of new insights from structural biology, computational biology, genomics, and proteomics to understand the etiology and pathogenesis of HIV-related disorders.
- Integrate studies of HIV-related disorders in the planning and conduct of treatment trials.

APPENDIX A:

NIH Institutes and Centers

NIH INSTITUTES AND CENTERS

NCI	National Cancer Institute
NEI	National Eye Institute
NHLBI	National Heart, Lung, and Blood Institute
NHGRI	National Human Genome Research Institute
NIA	National Institute on Aging
NIAAA	National Institute on Alcohol Abuse and Alcoholism
NIAID	National Institute of Allergy and Infectious Diseases
NIAMS	National Institute of Arthritis and Musculoskeletal and Skin Diseases
NICHD	National Institute of Child Health and Human Development
NIDCD	National Institute on Deafness and Other Communication Disorders
NIDCR	National Institute of Dental and Craniofacial Research
NIDDK	National Institute of Diabetes and Digestive and Kidney Diseases
NINDS	National Institute of Neurological Disorders and Stroke
NIDA	National Institute on Drug Abuse
NIEHS	National Institute of Environmental Health Sciences
NIGMS	National Institute of General Medical Sciences
NIMH	National Institute of Mental Health
NINR	National Institute of Nursing Research
NLM	National Library of Medicine
CC	Warren Grant Magnuson Clinical Center
CIT	Center for Information Technology
NCCAM	National Center for Complementary and Alternative Medicine
NCRR	National Center for Research Resources
FIC	Fogarty International Center
CSR	Center for Scientific Review
NCMHD	National Center on Minority Health and Health Disparities
NIBIB	National Institute of Biomedical Imaging and Bioengineering

APPENDIX B:

FY 2003 OAR Planning Group for Etiology and Pathogenesis

FY 2003 ETIOLOGY AND PATHOGENESIS PLANNING GROUP

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APPENDIX C:

List of Acronyms

LIST OF ACRONYMS

ART	antiretroviral therapy
ACTIS	AIDS Clinical Trials Information Service
AIDS	acquired immunodeficiency syndrome
AITRP	AIDS International Training and Research Program, FIC
ATI	Analytic Treatment Interruption
ATIS	HIV/AIDS Treatment Information Service
AVEG/HVTN	AIDS Vaccine Evaluation Group/HIV Vaccine Trials Network
BSL	biosafety level
B/START	Behavioral Science Track Award for Rapid Transition
CAB	community advisory board
CBO	community-based organizations
CDC	Centers for Disease Control and Prevention
CFAR	Centers for AIDS Research
CIPRA	Comprehensive International Programs in Research on AIDS
CMV	cytomegalovirus
CNS	central nervous system
CSF	cerebrospinal fluid
CTL	cytotoxic T lymphocytes
DC	dendritic cell
DHHS	Department of Health and Human Services
DNA	deoxyribonucleic acid
DOT	directly observed therapy
EBV	Epstein-Barr virus
FDA	Food and Drug Administration
FIRCA	Fogarty International Research Collaboration Award, FIC
GCP	Good Clinical Practices
GCRC	General Clinical Research Center
GI	gastrointestinal

GLP/GMP	good laboratory practices/good manufacturing production
HAART	highly active antiretroviral therapy
HBCU	Historically Black Colleges and Unviersities
HBV	hepatitis B virus
HCFA	Health Care Financing Administration
HCV	hepatitis C virus
HERS	HIV Epidemiology Research Study
HHV	human herpes virus
HIV	human immunodeficiency virus
HPTN	HIV Prevention Trial Network
HPV	human papillomavirus
HRSA	Health Resources and Services Administration
HVTN	HIV Vaccine Trials Network
IC	Institute and Center
ICC	invasive cervical cancer
IDU	injecting drug user
IHS	Indian Health Service
IUD	intrauterine device
JCV	JC virus
KS	Kaposi's sarcoma
KSHV	Kaposi's sarcoma herpes virus
LRP	Loan Repayment Program, NIH
MAC	*Mycobacterium avium* complex
MCT	mother-to-child transmission
MDR-TB	multiple drug-resistant tuberculosis
MHC	major histocompatibility complex
MSM	men who have sex with men
N9	nonoxynol
NAFEO	National Association for Equal Opportunity in Higher Education
NGO	nongovernment organizations

NHL	non-Hodgkin's lymphoma
NHP	non-human primate
NIH	National Institutes of Health
NRTIs	nucleoside reverse transcriptase inhibitors
OAR	Office of AIDS Research, NIH
OARAC	Office of AIDS Research Advisory Council
OD	Office of the Director, NIH
OI	opportunistic infection
PHS	Public Health Service
PML	progressive multifocal leukoencephalopathy
RCMI	Research Center in Minority Institution
RCT	randomized clinical trials
RFIP	Research Facilities Infrastructure Program
RNA	ribonucleic acid
RPRC	Regional Primate Research Center
SAMHSA	Substance Abuse and Mental Health Services Administration
SCID	severe combined immunodeficiency
SHIV	chimeric simian/human immunodeficiency virus
SIT	scheduled intermittent therapy
SIV	simian immunodeficiency virus
SPF	specific pathogen-free
STD	sexually transmitted disease
STI	Structured Treatment Interruption
TB	tuberculosis
TI	treatment interruption
UNAIDS	United Nations Joint Programme on AIDS
VEE	Venezuelan equine encephalitis virus
VRC	Vaccine Research Center
WHO	World Health Organization
WIHS	Women's Interagency HIV Study

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